Supplemental material I: Evaluation Guidelines

Initial evaluation [Tier I]

Tier I consists of six dichotomous questions (table 1). HOS are only suitable for QRA if all questions are answered affirmatively. A negative answer to one of the questions should result in exclusion of the HOS for QRA.

T1.1 Is the study design case-control, cohort or cross-sectional?

With the exception of rare examples such as asbestos-mesothelioma few exposures are exclusively related to a specific health effect(Swaen 2006). This situation underlines the desirability to approach experimental conditions as close as possible in HOS designs. An important aspect of experimental conditions is the ability to compare an observed effect to a reference situation. For HOS considered for QRA this has two implications. In order to discuss acceptable exposure levels or exposure thresholds studies need to include exposure contexts in which health effects are representative of background levels. In addition, the exposure levels of a group of individuals with similar observed health effects (cases) can only be interpreted if information on the exposure levels of individuals without the observed health effects (controls) is available. Therefore, HOS that do not include a relevant reference situation should not be used for QRA. In addition, HOS based on an ecological study design should not be used in QRA to avoid the ecological fallacy (Greenland and Robins 1994) . Consequently, the guidelines will focus on case-control, cohort or cross-sectional study designs.

T1.2 Is exposure expressed on a ratio scale and specific for the agent of interest?

To allow comparison of exposure-response relationships derived from multiple data sets in meta-analyses or systematic reviews exposure needs to be expressed on a ratio scale(Stevens

1946). Therefore, quantitative exposure measurements should be at the basis of exposure assessment. HOS that present quantitative exposure estimates based solely on expert judgment should not be used in QRA. The range of exposures that is reported in HOS has no direct bearing on the inclusion of HOS into QRA. A small range of exposures observed in a single study does indeed preclude the derivation of an exposure-response relation within that study. However, in combination with other studies such a study might provide valuable information regarding observed health effects at a specific point on the ratio scale. For QRA the exposure measures reported in HOS need to be specific for the agent of interest. Only a highly specific measure of exposure can be used to demonstrate a potential causal relation between exposure and health effect.

T1.3. Is a detailed description of the statistical analysis provided?

An accurate description of the applied statistical methods is essential for the interpretation of the results of HOS. Many different aspects contribute to the quality of the statistical analysis. In general, a good initial approach to the assessment of statistical analysis in HOS is to question whether enough details have been provided to allow replication of the analysis (provided that the crude data would be available). Without a sufficient detailed description of the statistical analysis it is impossible for risk assessors to assess the quality of statistical analysis and HOS should be excluded from QRA. A sufficiently described, but flawed, statistical analysis should also result in exclusion from QRA.

T1.4. Are criteria for inclusion of subjects into the study described with sufficient detail?

Without accurately defined inclusion criteria it is impossible to assess the impact of selection bias on the quality of HOS. Selection bias potentially could affect both internal and external validity of HOS (Delgado-Rodriguez and Llorca 2004). Therefore HOS that lack a

sufficiently detailed description of the subject inclusion criteria should be excluded from QRA.

T1.5. Is the assessment of the health effect performed with a validated method?

QRA requires objective assessment of health effects in HOS. Therefore health effects should be assessed according to recognized norms and the methods that are used for assessment should have been validated with a current 'best practice'. Studies that incorporate a clinically manifested disease as health endpoint should provide a detailed description of the definition that is used to classify the disease (e.g. ICD classification, pathological confirmation). Studies that incorporate an intermediate endpoint (e.g. chromosomal aberrations, blood pressure) should specify the laboratory methods used to quantify the endpoint as well as (if applicable) information on sample collection, timing of sample collection and storage of biological materials.

T1.6. Are all relevant potential strong confounding factors considered in the study design?

The possibility of confounding is a commonly used argument to point out the limitations of HOS. Confounding occurs when a factor associated to the health outcome and the exposure of interest modifies the observed study outcome (Checkoway 2004). Potential confounding factors can be identified based on previous epidemiological evidence and/or knowledge on the underlying pathophysiological process of the health effect of interest. When potential confounding factors are included in the study design, it is possible to test for the possible effect of confounders on the study outcome and if necessary to adjust study outcomes for this effect. It is important to realize that the impact of confounding factors on the study outcome is only substantial when the association with the health outcome and exposure of interest is strong (Blair et al. 2007). As such HOS should only be excluded when there is convincing

evidence that a factor is a potential strong confounder of the exposure-response relation of interest and the factor is not considered in the HOS. In addition, if one assumes that there is not a strong probability of imbalance between study groups for a potentially strong confounder, (e.g. RR>5), non-inclusion of the confounder in the study design study should not be a basis for exclusion for QRA(Blair et al. 2007).

Categorization of the study [Tier II]

The categorization of HOS based on the type of study design (table 1) is used to exclude HOS and to select the appropriate criteria for evaluation in tier III.

T2.1 Type of study design:

To determine whether the type of study design is appropriate for QRA risk assessors need to make an assumption on the nature of the exposure-response relation of interest. The assumed nature of exposure-response relation determines whether a longitudinal component is necessary in the study design in order to be able to detect a potential response resulting from the exposure of interest. If it is decided that a longitudinal component is required cross-sectional study designs should be excluded from QRA. Study designs with a longitudinal component are categorized into case-control (including case-cohort, and nested case-control studies) or cohort designs.

Design specific evaluation [Tier III]

In tier III (table 1) guidelines for the design specific evaluation of HOS are listed. A distinction is made between the criteria that are intended to assess whether HOS are suitable for QRA and the criteria that are intended to be used in ranking of the HOS suitable for QRA based on the quality of these HOS. Criteria 3.2-3.5 (table 1) are intended to be used in both

the selection and ranking of HOS. For an objective and transparent evaluation decisions concerning acceptable levels for these criteria should be made *a priori* to the evaluation. To provide an example of this approach we consider the response rate of a study. If a risk assessor decides that the acceptable level of the response rate is 80 % all studies with a response rate < 80% should be excluded from QRA. For studies with a response rate 80% - 100 % the response rate should be used in the ranking based on study quality.

T3.1 Response rate

A low response rate has a large effect on the potential for bias in HOS and therefore affects the quality of HOS(Delgado-Rodriguez and Llorca 2004; Hernan et al. 2004; Mezei and Kheifets 2006; Pearce et al. 2007). The potential effect of a low response rate on bias in HOS has been demonstrated by Callahan et al(Callahan et al. 1995). In their example a disease prevalence of 20% is assumed. With a response rate of 90% the potential bias ranged from -9% to +2 %. However the potential bias increased to -20% to +13% when the response rate was reduced to 60%(Callahan et al. 1995). Aspects that contribute to the impact of response rate on the estimated risks are the 'true' prevalence of the studied health effect and the underlying causes for the low response rate. For an objective evaluation it is important that risk assessors define a minimum acceptable response rate *a priori* to evaluation of HOS. However, an exception should be made for studies that report a response rate below the minimum acceptable response rate but are able to demonstrate that the studied population is representative for the population of interest, e.g. with a non-response analysis.

T3.2 Loss to follow-up

A high loss to follow-up is in many ways comparable to low response rate. The mechanism causing loss to follow-up and the 'true' prevalence of a studied health effect determine the

potential impact of loss to follow-up on estimated risk levels(Blanker et al. 2005; Kristman et al. 2004; Zunzunegui et al. 2001). Therefore the approach to the evaluation of loss to follow-up is the same as the approach to the response rate. Again, for objective evaluation it is important that risk assessors define maximum acceptable loss to follow-up *a priori* to evaluation of HOS.

T3.3 Minimum follow-up time

The follow-up time in a study should be based on the estimated latency between exposure and the development of a health effect. For most chronic health effects, especially certain cancer types, considerable latency is expected between exposure and disease. For example, a study by Agalliu et al. explored the latency between exposure to metalworking fluids and prostate cancer incidence and suggested that a latency period of 25 years was plausible(Agalliu et al. 2005). While the exact latency between exposure and occurrence of a health effect is usually not known it is clear that insufficient follow-up time will certainly lead to a considerable bias in the exposure response relation. Therefore, studies that have not incorporated sufficient follow-up time should be excluded from QRA.

T3.4 Quality of the exposure measurement methods

Quantitative measurements used in exposure assessment in HOS can potentially differ with regards to the quality of the measurement methods and the analytical methods that have been used. A guideline to evaluate HOS based on the quality of exposure measurements is to compare the method(s) used in the study under evaluation to the method(s) that are currently considered as best practice. Some studies provide information on side by side comparisons of the used exposure measurement method with the best practice at the time of the study. Additional information from studies that solely focus on side by side comparisons of exposure

measurement methods can be used as well(de Vocht et al. 2006; Stephenson et al. 2004). If there is solid evidence that a specific method is unable to provide high quality exposure measurements HOS that used this method in their exposure assessment strategy should not be used for QRA.

T3.5 Insight in the variability of the exposure

For the evaluation of HOS it is important to realize that the exposure measurements used in exposure assessment can be highly variable. This variability can be attributed to a combination of measurement error and variation in exposure levels over time and space. Classical measurement error, by which analytical and sampling error is covered, usually only plays a marginal role because its magnitude is often orders of magnitude smaller than the variability in exposure over time and space. It is therefore preferred to use the terminology variability in exposure instead of measurement error although the effect of the variability on measures of associations between exposure and disease is a measurement error issue. The influence of exposure variability is dependent on the exposure assessment strategy. Simply speaking two quantitative exposure assessment strategies exist, measurements for each individual in the population or measurements for so called homogeneous exposure categories(Armstrong 1990). Often, exposure assessment on the individual level is considered the gold standard. However, this strategy is most sensitive to intra-individual variability of the exposure. If intra-individual variability is not correctly addressed in an individual based exposure assessment strategy strong underestimation of the exposure response relationship might occur when this variability is large relative to the variability between individuals in the population. However, this underestimation becomes smaller when more repeated measurements per individual have been taken(Heederik and Attfield 2000). Categorization of the population in *a priori* assigned exposure groups, and use of the measured average

exposure per exposure group in an exposure response relationship is less sensitive for intra-individual variability. In most cases this strategy is known to lead to unbiased relations between exposure and response, however, unexplained differences in health risks within exposure groups and unaddressed differences in exposure levels within exposure groups can lead to a reduction of power of this strategy in comparison with the individual exposure assessment strategy(Tielemans et al. 1998). Advanced methodologies to acquire insight in the level of measurement variability on HOS outcomes have been proposed (Heederik and Miller 1988; Kromhout et al. 1999; Loomis et al. 1998; Xue et al. 2006). *A priori* to the evaluation risk assessors need to define a minimum acceptable level of information that is required to be able to assess whether enough insight in variability of exposure measurements is provided in HOS. Tielemans et al have developed guidelines to evaluate exposure data from HOS performed in the occupational exposure context(Tielemans et al. 2002). Similar approaches should be applied to exposure data from other exposure contexts. Differences between HOS in the ability to assess the relative contribution of the different sources of variability in exposure measurements can be used to rank the HOS. One should also realize that the two examples given above of individual exposure assessment and categorization approaches are only two contrasting examples out of a wide range of exposure assessment strategies. Specific theory exists for other exposure metrics and specific situations such as conversion of exposure measured on a continuous scale into exposure categories, unmeasured exposure correlated to the measured exposure, et cetera(Dosemeci et al. 1990; Loomis and Savitz 1994). For specific situations the theoretical background needs to be considered in detail to evaluate a strategy.

T3.6 Application of exposure measurements in the exposure assessment

In most HOS researchers are confronted with a scarcity of exposure measurements. As a result exposure measurements might not be available for each 'assignment unit' (e.g. a single

individual or a group of individuals with assumed similar exposure patterns) for the complete time period of interest. In this situation exposure measurements performed for 'assignment-unit-time-period' combinations and information regarding the circumstances of these measurements (e.g. year of measurement, type of weather during measurement or the task the measured individual performed during the measurement) is used to estimate exposure levels for 'assignment-unit-time-period' combinations for which exposure measurements are not available. The strategy that is used to extrapolate measurements over assignment-unit-time-period combinations determines the validity of the exposure estimates and therefore has a large impact on the overall quality of the quantification of exposure. In most HOS exposure measurements are extrapolated following a set of decision rules based on expert judgment. The use of expert judgment requires that a complete and detailed insight in the applied decision rules is essential for evaluation of HOS.

T3.7 Type of exposure metric

In an ideal situation an exposure metric captures three aspects that determine exposure: intensity, duration and timing (Vacek 1997). The quality of an exposure metric is based on biological considerations such as the time window of exposure that is relevant to the health effect of interest (Loomis et al. 1998; Seixas et al. 1993; Vacek 1997). A guideline to evaluate HOS based on the used exposure metric is to compare the used metric with the current state of knowledge on the nature of the relation between the exposure and health outcome of interest.

T3.8 Specificity of the exposure indicator

In situations where it is difficult to assess the actual exposure that is assumed to be causally related to the health effect of interest, a '*causal'* indicator of exposure, researchers might assess a '*proxy*' for the causal exposure. However, it is crucial that the proxy exposure is

highly correlated to the exposure of interest. An example of the use of an exposure proxy is the use of elemental carbon as proxy for exposure to diesel engine exhausts(Schauer 2003). Once absorbed in the human body distribution, metabolism and excretion have a large impact on the dose of a specific agent (or metabolite) at the site of action. Given they can be measured accurately, application of exposure indicators capable of incorporating these biological influences in exposure estimates will result in increased correlation between the exposure indicator and the dose at the site of action. The application of biomarkers of exposure in HOS potentially provides the possibility to obtain exposure indicators with higher specificity compared to indicators of external exposure. Similar, as with external exposure, insight in variability of biomarker based exposure measurements is of utmost importance for QRA. We suggest a categorization of exposure indicators based on two decisions '*proxy'* vs. '*causal'* indicator of exposure and '*external'* vs. '*internal'* indicator of exposure. Although the exposure indicator combination '*causal-internal'* in theory provides the highest quality of evidence for QRA the actual quality will still depend on the assumed accuracy of the exposure measurement/classification based on the level of insight in the variability of exposure.

T3.9 Blinded exposure assessment

To avoid that observer bias occurs exposure assessment should always be performed blinded for the health outcome of interest. If exposure assessment was performed on the individual level, omission of a statement regarding blinded exposure assessment is a reason to exclude HOS from QRA. If exposure assessment was performed to assess exposure for a priori defined 'homogeneous exposure categories', there is no direct connection between the individuals in the study population and the exposure assessment and therefore this criterion needs less stringent application.

T3.10 Quality of the exposure assignment strategy

In the exposure assignment step exposure levels assessed for specific 'assignment-unit-time-period' combinations are translated into exposure estimates for each individual in the study population. Assignment is based on information that is related to the individuals in the study population and related to the 'assignment-unit-time-period' combinations for which exposure levels have been assessed. Examples of this information are the jobs an individual performed during his working career, a description of daily diet or information on other factors potentially affecting exposure levels. The exposure context in which HOS are performed determines which type of information is available for exposure assignment. A proper evaluation of the quality of exposure assignment requires insight in the proportion of the 'assignment-unit-time-period' combinations used for assignment for which no or little exposure measurements were available and exposure levels had to be inferred. In addition, the overlap between the 'assignment-unit-time-period' combinations for which exposure measurements were available and the exposure time periods that are assumed to be relevant to the assessed health risk needs to be evaluated. Miller et al. have demonstrated that, if enough information is available, differences with regards to the use of measurement data in exposure assignment can be made evident with the use of a simple tool (Miller et al. 2005). In this example the availability of exposure measurements was directly compared to the distribution of person years in the study population. However, a more detailed analysis on the level of 'assignment-unit-time-period' combinations is needed to provide a more accurate insight in the quality of exposure assignment. While a high quality exposure assignment strategy contributes considerably to the quality of the evidence from HOS, at this moment, most HOS do not provide enough information to enable such a detailed evaluation.

T3.11 Potential for information bias

In studies in which potentially more detailed information is available for cases than for controls or in cohort studies in which an index population is compared to a reference population there is a potential for information bias. Information bias has a large impact on HOS study outcomes and therefore on the quality of the evidence from HOS for QRA(Delgado-Rodriguez and Llorca 2004). A large potential for information bias in HOS will result in a decrease in the potential weight of evidence for QRA and should therefore be used in the ranking of HOS based on quality.

T3.12 Blinded health outcome assessment

Blinded determination of health outcomes in HOS regardless of the exposure status of the observed individual reduces the probability of observer bias in the study results. Non-blinded health outcome assessment should result in exclusion from QRA.

T3.13 Insight in the potential for systematic error in the study results

Most HOS provide statistics such as confidence intervals surrounding an estimate or *p* values for the interpretation of sampling error in the study results. However, these statistics do not provide insight in the potential for systematic error in study results. A more sophisticated approach to acquire insight into the potential for systematic error in a HOS is to perform sensitivity analyses. The basic idea of a sensitivity analysis is to quantify the uncertainty in the estimated effect based on insight in the possible variation of all sources that contribute to systematic error in a study. To quantify this uncertainty one needs to define an overall structure that relates all the individual sources of systematic error to the study outcome(Lash and Fink 2003). Insight in the potential for systematic error in study results contributes to the quality of HOS.

References:

Agalliu I, Kriebel D, Quinn MM, Wegman DH, Eisen EA. 2005. Prostate cancer incidence in relation to time windows of exposure to metalworking fluids in the auto industry. Epidemiology 16(5):664-671.

Armstrong BG. 1990. The effects of measurement errors on relative risk regressions. Am J Epidemiol 132(6):1176-1184.

Blair A, Stewart P, Lubin JH, Forastiere F. 2007. Methodological issues regarding confounding and exposure misclassification in epidemiological studies of occupational exposures. Am J Ind Med 50(3):199-207.

Blanker MH, Prins J, Bosch JL, Schouten BW, Bernsen RM, Groeneveld FP, et al. 2005. Loss to follow-up in a longitudinal study on urogenital tract symptoms in Dutch older men. Urol Int 75(1):30-37.

Callahan MA, Clickner RP, Whitmore RW, Kalton G, Sexton K. 1995. Overview of important design issues for a National Human Exposure Assessment Survey. J Expo Anal Environ Epidemiol 5(3):257-282.

Checkoway H. 2004. Case-crossover designs in occupational health. Occup Environ Med 61(12):953-954.

de Vocht F, Huizer D, Prause M, Jakobsson K, Peplonska B, Straif K, et al. 2006. Field comparison of inhalable aerosol samplers applied in the european rubber manufacturing industry. Int Arch Occup Environ Health 79(8):621-629.

Delgado-Rodriguez M, Llorca J. 2004. Bias. J Epidemiol Community Health 58(8):635-641.

Dosemeci M, Wacholder S, Lubin JH. 1990. Does nondifferential misclassification of exposure always bias a true effect toward the null value? Am J Epidemiol 132(4):746-748.

Greenland S, Robins J. 1994. Invited commentary: ecologic studies--biases, misconceptions, and counterexamples. Am J Epidemiol 139(8):747-760.

Heederik D, Attfield M. 2000. Characterization of dust exposure for the study of chronic occupational lung disease: a comparison of different exposure assessment strategies. Am J Epidemiol 151(10):982-990.

Heederik D, Miller BG. 1988. Weak associations in occupational epidemiology: adjustment for exposure estimation error. Int J Epidemiol 17(4):970-974.

Hernan MA, Hernandez-Diaz S, Robins JM. 2004. A structural approach to selection bias. Epidemiology 15(5):615-625.

Kristman V, Manno M, Cote P. 2004. Loss to follow-up in cohort studies: how much is too much? Eur J Epidemiol 19(8):751-760.

Kromhout H, Loomis DP, Kleckner RC. 1999. Uncertainty in the relation between exposure to magnetic fields and brain cancer due to assessment and assignment of exposure and analytical methods in dose-response modeling. Ann N Y Acad Sci 895:141-155.

Lash TL, Fink AK. 2003. Semi-automated sensitivity analysis to assess systematic errors in observational data. Epidemiology 14(4):451-458.

Loomis A, Kromhout H, Kleckner RC, Savitz DA. 1998. Effects of the analytical treatment of exposure data on associations of cancer and occupational magnetic field exposure. Am J Ind Med 34(1):49-56.

Loomis DP, Savitz DA. 1994. Effect of incomplete exposure assessment on epidemiologic dose-response analyses. Scand J Work Environ Health 20(3):200-205.

Mezei G, Kheifets L. 2006. Selection bias and its implications for case-control studies: a case study of magnetic field exposure and childhood leukaemia. Int J Epidemiol 35(2):397-406.

Miller B, Fransman W, Heederik D, Hurley J, Kromhout H, Fitzsimons E. 2005. A review of the data quality and comparability of case-control studies of low-level exposure to benzene in the petroleum industry. Edinburgh: Institute of Occupational Medicine.

Pearce N, Checkoway H, Kriebel D. 2007. Bias in occupational epidemiology studies. Occup Environ Med 64(8):562-568.

Schauer JJ. 2003. Evaluation of elemental carbon as a marker for diesel particulate matter. J Expo Anal Environ Epidemiol 13(6):443-453.

Seixas NS, Robins TG, Becker M. 1993. A novel approach to the characterization of cumulative exposure for the study of chronic occupational disease. Am J Epidemiol 137(4):463-471.

Stephenson DJ, Lillquist DR, DeRosso FD, Greene DD, White G. 2004. Side-by-side comparison of three sampling methods for aerosolized endotoxin in a wastewater treatment facility. J Environ Health 67(4):16-19.

Stevens SS. 1946. On the Theory of Scales of Measurement. Science 103(2684):677-680.

Swaen GM. 2006. A framework for using epidemiological data for risk assessment. Hum Exp Toxicol 25(3):147-155.

Tielemans E, Kupper LL, Kromhout H, Heederik D, Houba R. 1998. Individual-based and group-based occupational exposure assessment: some equations to evaluate different strategies. Ann Occup Hyg 42(2):115-119.

Tielemans E, Marquart H, De Cock J, Groenewold M, Van Hemmen J. 2002. A proposal for evaluation of exposure data. Ann Occup Hyg 46(3):287-297.

Vacek PM. 1997. Assessing the effect of intensity when exposure varies over time. Stat Med 16(5):505-513.

Xue X, Kim MY, Shore RE. 2006. Estimation of health risks associated with occupational radiation exposure: addressing measurement error and minimum detectable exposure level. Health Phys 91(6):582-591.

Zunzunegui MV, Beland F, Gutierrez-Cuadra P. 2001. Loss to follow-up in a longitudinal study on aging in Spain. J Clin Epidemiol 54(5):501-510.

Supplemental Material II : Selection of Studies that are Eligible for Application of the Evaluation Guidelines

Publications eligible for evaluation were identified as follows: 81 publications were identified with a Pubmed search which included the following MESH keywords *benzene, humans, leukemia* in combination with either *cohort studies* or case-*control studies*, 12 publications were added by following references included in a literature review that was identified in the original Pubmed search (Schnatter et al. 2005), finally 23 publications were added by following references included in regulatory risk assessments by the Canadian Centre for Occupational Health and Safety (CCOHS, 1995), the U.S. National institute for Occupation and Health (NIOSH, 1976), the U.S. Agency for Toxic Substances and Disease Registry (ATSDR, 2007) and the U.S. Environmental Protection Agency (EPA, 1998). All the identified publications were reviewed for eligibility of application of the evaluation guidelines (*table 1)*. For one of the study populations (the Pliofilm cohort) several re-analyses were performed (Crump 1994; Crump 1996; Paustenbach et al. 1992) These re-analyses were based on sets of exposure estimates that were different from the publications on this cohort by the principal investigators. Because the discussion on which exposure estimates were 'best' remains unresolved and because only publications based on one of the sets of exposure estimates should be included in QRA, we chose to include only publications that were based on the original exposure estimates (Rinsky 1989; Rinsky et al. 1981). Additionally, two other re-analyses of the pliofilm data were excluded from evaluation as well (Finkelstein 2000; Schnatter et al. 1996). Preference was given to the analyses performed in the original publications on this cohort, which were more compatible to the analyses performed in the other included publications. 32 publications were found not eligible because results from hazard characterization were not reported. From the 84 publication that did report results from hazard characterization, 53 publications were excluded because no quantitative exposure-

response analysis specific for benzene and leukemia was reported. Finally 22 publications did not report results from quantitative exposure-response analysis specific for benzene and AML.

References:

ATSDR (U.S. Agency for Toxic Substances and Disease Registry). 2007. Toxicological profile for benzene. Available: http://www.atsdr.cdc.gov/toxprofiles/tp3.pdf [accessed 12 February 2008].

CCOHS (Canadian Centre for Occupational Health and Safety). 1995. Report to the occupational disease panel (Industrial Disease Standards Panel) on occupational exposure to benzene and leukaemia. Available: http://www.canoshweb.org/odp/html/rp7.htm [accessed 12 February 2008].

Crump KS. 1994. Risk of benzene-induced leukemia: a sensitivity analysis of the pliofilm cohort with additional follow-up and new exposure estimates. J Toxicol Environ Health 42(2):219-242.

Crump KS. 1996. Risk of benzene-induced leukemia predicted from the Pliofilm cohort. Environ Health Perspect 104 Suppl 6:1437-1441.

EPA (U.S. Environmental protection agency). 1998. Carcinogenic Effects of Benzene: an Update. Available: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=2806 [accessed 12 February 2008].

Finkelstein MM. 2000. Leukemia after exposure to benzene: temporal trends and implications for standards. Am J Ind Med 38(1):1-7.

NIOSH (U.S. National Institute for Occupational Safety and Health). 1976. Revised recommendation for an occupational exposure standard for benzene. Available: http://www.cdc.gov/niosh/pdfs/76-benz.pdf [accessed 12 February 2008].

Paustenbach DJ, Price PS, Ollison W, Blank C, Jernigan JD, Bass RD, et al. 1992. Reevaluation of benzene exposure for the Pliofilm (rubberworker) cohort (1936-1976). J Toxicol Environ Health 36(3):177-231.

Rinsky RA. 1989. Benzene and leukemia: an epidemiologic risk assessment. Environ Health Perspect 82:189-191.

Rinsky RA, Young RJ, Smith AB. 1981. Leukemia in benzene workers. Am J Ind Med 2(3):217-245.

Schnatter AR, Nicolich MJ, Bird MG. 1996. Determination of leukemogenic benzene exposure concentrations: refined analyses of the Pliofilm cohort. Risk Anal 16(6):833-840.

Schnatter AR, Rosamilia K, Wojcik NC. 2005. Review of the literature on benzene exposure and leukemia subtypes. Chem Biol Interact 153-154:9-21.

Supplemental Material, Table 1 Overview identified studies.

	Citation	Hazard characterization	Quantitative exposure-response analysis specific for benzene and leukemia	Quantitative exposure-response analysis specific for benzene and AML	Included in the evaluation	Remarks	Source
1	Girard, R. & Revol, L. La frequence d'une exposition benzenique au cours des hempathies graves. Nouv Rev Fr Hematol 10, 477-83 (1970).	YES	NO		NO		a
2	Ishimaru, T. et al. Occupational factors in the epidemiology of leukemia in Hiroshima and Nagasaki. Am J Epidemiol 93, 157-65 (1971).	YES	NO		NO		a
3	Aksoy, M., Erdem, S. & DinCol, G. Leukemia in shoe-workers exposed chronically to benzene. Blood 44, 837-41 (1974).	YES	NO		NO		b
4	Thorpe, J. J. Epidemiologic survey of leukemia in persons potentially exposed to benzene. J Occup Med 16, 375-82 (1974).	YES	NO		NO		c
5	McMichael, A. J., Spirtas, R., Kupper, L. L. & Gamble, J. F. Solvent exposure and leukemia among rubber workers: an epidemiologic study. J Occup Med 17, 234-9 (1975).	YES	NO		NO		c
6	Brown, S. M. Letters to the editor: Leukemia and potential benzene exposure. J Occup Med 17, 5-6 (1975).	NO			NO		d
7	McMichael, A. J., Spirtas, R., Gamble, J. & Tousey, P. Mortality among rubber workers-Relationship to specific jobs. J Occup Med 18, 178-185 (1976).	YES	NO		NO		c
8	Infante, P. F., Rinsky, R. A., Wagoner, J. K. & Young, R. J. Leukaemia in benzene workers. Lancet 2, 76-8 (1977).	YES	NO		NO		d
9	Aksoy, M. & Erdem, S. Followup study on the mortality and the development of leukemia in 44 pancytopenic patients with chronic exposure to benzene. Blood 52, 285-92 (1978).	YES	NO		NO		d
10	Brandt, L., Nilsson, P. G. & Mitelman, F. Occupational exposure to petroleum products in men with acute non-lymphocytic leukaemia. Br Med J 1, 553 (1978).	YES	NO		NO		a
11	Infante, P. F. Leukemia among workers exposed to benzene. Tex Rep Biol Med 37, 153-61 (1978).	YES	NO		NO		e

	Citation	Hazard characterization	Quantitative exposure-response analysis specific for benzene and leukemia	Quantitative exposure-response analysis specific for benzene and AML	Included in the evaluation	Remarks	Source
12	Nicholson, W. J., Selikoff, I. J. & Seidman, H. Mortality experience of styrene-polystyrene polymerization workers. Initial findings. Scand J Work Environ Health 4 Suppl 2, 247-52 (1978).	YES	NO		NO		d
13	Ott, M. G., Townsend, J. C., Fishbeck, W. A. & Langner, R. A. Mortality among individuals occupationally exposed to benzene. Arch Environ Health 33, 3-10 (1978).	YES	YES	NO	NO		d
14	Linos, A., Kyle, R. A., O'Fallon, W. M. & Kurland, L. T. A case-control study of occupational exposures and leukaemia. Int J Epidemiol 9, 131-5 (1980).	YES	NO		NO		b
15	Ott, M. G., Kolesar, R. C., Scharnweber, H. C., Schneider, E. J. & Venable, J. R. A mortality survey of employees engaged in the development or manufacture of styrene-based products. J Occup Med 22, 445-60 (1980).	YES	NO		NO		d
16	Rinsky, R. A., Young, R. J. & Smith, A. B. Leukemia in benzene workers. Am J Ind Med 2, 217-45 (1981).	YES	NO		NO		d
17	Rushton, L. & Alderson, M. R. A case-control study to investigate the association between exposure to benzene and deaths from leukaemia in oil refinery workers. Br J Cancer 43, 77-84 (1981).	YES	NO		NO		a
18	Schottenfeld, D., Warshauer, M. & Zauber, A. in Quantification of Occupational Cancer (eds. R, P. & M, S.) (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1981).	YES	NO		NO		a
19	Thomas, T. L., Waxweiler, R. J., Moure-Eraso, R., Itaya, S. & Fraumeni, J. F., Jr. Mortality patterns among workers in three Texas oil refineries. J Occup Med 24, 135-41 (1982).	YES	NO		NO		a
20	Arp, E. W., Jr., Wolf, P. H. & Checkoway, H. Lymphocytic leukemia and exposures to benzene and other solvents in the rubber industry. J Occup Med 25, 598-602 (1983).	YES	NO		NO		a
21	Decoufle, P., Blattner, W. A. & Blair, A. Mortality among chemical workers exposed to benzene and other agents. Environ Res 30, 16-25 (1983).	YES	NO		NO		b

	Citation	Hazard characterization	Quantitative exposure-response analysis specific for benzene and leukemia	Quantitative exposure-response analysis specific for benzene and AML	Included in the evaluation	Remarks	Source
22	Tsai, S. P. et al. Retrospective mortality and medical surveillance studies of workers in benzene areas of refineries. J Occup Med 25, 685-92 (1983).	YES	NO		NO		b
23	Checkoway, H., Wilcosky, T., Wolf, P. & Tyroler, H. An evaluation of the associations of leukemia and rubber industry solvent exposures. Am J Ind Med 5, 239-49 (1984).	YES	NO		NO		a
24	Shaw, G., Lavey, R., Jackson, R. & Austin, D. Association of childhood leukemia with maternal age, birth order, and paternal occupation. A case-control study. Am J Epidemiol 119, 788-95 (1984).	YES	NO		NO		d
25	Austin, H. & Cole, P. Cigarette smoking and leukemia. J Chronic Dis 39, 417-21 (1986).	NO			NO		d
26	Austin, H., Cole, P. & McCraw, D. S. A case-control study of leukemia at an oil refinery. J Occup Med 28, 1169-73 (1986).	NO			NO		d
27	Bond, G. G., McLaren, E. A., Baldwin, C. L. & Cook, R. R. An update of mortality among chemical workers exposed to benzene. Br J Ind Med 43, 685-91 (1986).	YES	YES	NO	NO	2004 update is included	a
28	Flodin, U., Fredriksson, M., Persson, B., Hardell, L. & Axelson, O. Background radiation, electrical work, and some other exposures associated with acute myeloid leukemia in a case-referent study. Arch Environ Health 41, 77-84 (1986).	YES	NO		NO		b
29	Linet, M. S., Stewart, W. F., Van Natta, M. L., McCaffrey, L. D. & Szklo, M. Comparison of methods for determining occupational exposure in a case-control interview study of chronic lymphocytic leukemia. J Occup Med 29, 136-41 (1987).	YES	NO		NO		b
30	Rinsky, R. A. et al. Benzene and leukemia. An epidemiologic risk assessment. N Engl J Med 316, 1044-50 (1987).	YES	YES	NO	NO		a
31	Wong, O. An industry wide mortality study of chemical workers occupationally exposed to benzene. II. Dose response analyses. Br J Ind Med 44, 382-95 (1987).	YES	YES	NO	NO		a
32	Wong, O. An industry wide mortality study of	YES	NO	NO	NO		a

	Citation	Hazard characterization	Quantitative exposure-response analysis specific for benzene and leukemia	Quantitative exposure-response analysis specific for benzene and AML	Included in the evaluation	Remarks	Source
	chemical workers occupationally exposed to benzene. I. General results. Br J Ind Med 44, 365-81 (1987).						
33	Yin, S. N. et al. Leukaemia in benzene workers: a retrospective cohort study. Br J Ind Med 44, 124-8 (1987).	YES	NO		NO		d
34	Malone, K. E. et al. Chronic lymphocytic leukemia in relation to chemical exposures. Am J Epidemiol 130, 1152-8 (1989).	YES	NO		NO		b
35	Paci, E. et al. Aplastic anemia, leukemia and other cancer mortality in a cohort of shoe workers exposed to benzene. Scand J Work Environ Health 15, 313-8 (1989).	YES	NO		NO		a
36	Rinsky, R. A. Benzene and leukemia: an epidemiologic risk assessment. Environ Health Perspect 82, 189-91 (1989).	YES	YES	NO	NO		d
37	Rinsky, R. A., Hornung, R. W. & Landrigan, P. J. Re: "Benzene and Leukemia: a Review of the Literature and a Risk Assessment". Am J Epidemiol 129, 1084-6 (1989).	NO			NO		d
38	Vai, T. et al. [A follow-up study of 304 cases of suspected pathology caused by benzene seen in 1950-71]. Med Lav 80, 397-404 (1989).	YES	NO		NO		d
39	Wongsrichanalai, C., Delzell, E. & Cole, P. Mortality from leukemia and other diseases among workers at a petroleum refinery. J Occup Med 31, 106-11 (1989).	YES	NO		NO		a
40	Yin, S. N. et al. A retrospective cohort study of leukemia and other cancers in benzene workers. Environ Health Perspect 82, 207-13 (1989).	YES	NO		NO		d
41	Young, N. Benzene and lymphoma. Am J Ind Med 15, 495-8 (1989).	NO			NO	Editorial	d
42	Collins, J. J. et al. A study of the hematologic effects of chronic low-level exposure to benzene. J Occup Med 33, 619-26 (1991).	YES	NO		NO		e
43	Hurley, J. F., Cherrie, J. W. & Maclaren, W. Exposure to benzene and mortality from leukaemia: results from coke oven and other coal product workers. Br J Ind Med 48, 502-3 (1991).	YES	NO		NO		d

	Citation	Hazard characterization	Quantitative exposure-response analysis specific for benzene and leukemia	Quantitative exposure-response analysis specific for benzene and AML	Included in the evaluation	Remarks	Source
44	McKinney, P. A., Alexander, F. E., Cartwright, R. A. & Parker, L. Parental occupations of children with leukaemia in west Cumbria, north Humberside, and Gateshead. Bmj 302, 681-7 (1991).	YES	NO		NO		d
45	Crane, M. M., Godwin, J. E., Annegers, J. F. & Keating, M. J. Is histological subtype a marker for environmental exposures in acute myelogenous leukemia? Cancer Epidemiol Biomarkers Prev 1, 183-8 (1992).	YES	NO		NO		d
46	Hayes, R. B. Biomarkers in occupational cancer epidemiology: considerations in study design. Environ Health Perspect 98, 149-54 (1992).	NO			NO		d
47	Heineman, E. F. et al. Occupational risk factors for multiple myeloma among Danish men. Cancer Causes Control 3, 555-68 (1992).	YES	YES	NO	NO		
48	Jakobsson, R., Ahlbom, A., Bellander, T. & Lundberg, I. [Follow-up of leukemia in drivers is of interest]. Lakartidningen 89, 1557 (1992).	NO			NO		d
49	Paustenbach, D. J. et al. Reevaluation of benzene exposure for the Pliofilm (rubberworker) cohort (1936-1976). J Toxicol Environ Health 36, 177-231 (1992).	YES	YES	NO	NO	This publication did not use the Rinksy exposure estimates and was therefore not considered in the evaluation	f
50	Richardson, S. et al. Occupational risk factors for acute leukaemia: a case-control study. Int J Epidemiol 21, 1063-73 (1992).	YES	NO		NO		b
51	Ciccone, G. et al. Myeloid leukemias and myelodysplastic syndromes: chemical exposure, histologic subtype and cytogenetics in a case-control study. Cancer Genet Cytogenet 68, 135-9 (1993).	YES	NO		NO		d
52	Schnatter, A. R., Katz, A. M., Nicolich, M. J. & Theriault, G. A retrospective mortality study among Canadian petroleum marketing and distribution workers. Environ Health Perspect 101 Suppl 6, 85-99 (1993).	YES	NO		NO		a
53	Crump, K. S. Risk of benzene-induced leukemia: a	YES	YES	NO	NO	This publication did not	d

	Citation	Hazard characterization	Quantitative exposure-response analysis specific for benzene and leukemia	Quantitative exposure-response analysis specific for benzene and AML	Included in the evaluation	Remarks	Source
	sensitivity analysis of the pliofilm cohort with additional follow-up and new exposure estimates. J Toxicol Environ Health 42, 219-42 (1994).					use the Rinksy exposure estimates and was therefore not considered in the evaluation	
54	Li, G. L. et al. Gender differences in hematopoietic and lymphoproliferative disorders and other cancer risks by major occupational group among workers exposed to benzene in China. J Occup Med 36, 875-81 (1994).	YES	NO		NO		d
55	Paxton, M. B., Chinchilli, V. M., Brett, S. M. & Rodricks, J. V. Leukemia risk associated with benzene exposure in the pliofilm cohort. II. Risk estimates. Risk Anal 14, 155-61 (1994).	YES	YES	NO	NO		d
56	Paxton, M. B., Chinchilli, V. M., Brett, S. M. & Rodricks, J. V. Leukemia risk associated with benzene exposure in the pliofilm cohort: I. Mortality update and exposure distribution. Risk Anal 14, 147-54 (1994).	NO			NO		d
57	Travis, L. B. et al. Hematopoietic malignancies and related disorders among benzene-exposed workers in China. Leuk Lymphoma 14, 91-102 (1994).	NO			NO		d
58	Bithell, J. F. & Draper, G. J. Apparent association between benzene and childhood leukaemia: methodological doubts concerning a report by Knox. J Epidemiol Community Health 49, 437-9 (1995).	NO			NO		d
59	Mele, A. et al. Epidemiology of acute promyelocytic leukemia. Haematologica 80, 405-8 (1995).	YES	NO		NO		d
60	Utterback, D. F. & Rinsky, R. A. Benzene exposure assessment in rubber hydrochloride workers: a critical evaluation of previous estimates. Am J Ind Med 27, 661-76 (1995).	NO			NO		d
61	**Wong, O. Risk of acute myeloid leukaemia and multiple myeloma in workers exposed to benzene. Occup Environ Med 52, 380-4 (1995).**	**YES**	**YES**	**YES**	**YES**		**d**
62	Wong, O. & Raabe, G. K. Cell-type-specific leukemia analyses in a combined cohort of more	NO			NO	Pooled analysis	d

	Citation	Hazard characterization	Quantitative exposure-response analysis specific for benzene and leukemia	Quantitative exposure-response analysis specific for benzene and AML	Included in the evaluation	Remarks	Source
	than 208,000 petroleum workers in the United States and the United Kingdom, 1937-1989. Regul Toxicol Pharmacol 21, 307-21 (1995).						
63	Armstrong, T. W. et al. Retrospective benzene and total hydrocarbon exposure assessment for a petroleum marketing and distribution worker epidemiology study. Am Ind Hyg Assoc J 57, 333-43 (1996).	NO			NO		d
64	Clavel, J. et al. Hairy cell leukaemia and occupational exposure to benzene. Occup Environ Med 53, 533-9 (1996).	YES	YES	NO	NO		d
65	Crump, K. S. Risk of benzene-induced leukemia predicted from the Pliofilm cohort. Environ Health Perspect 104 Suppl 6, 1437-41 (1996).	YES			NO	This publication did not use the Rinksy exposure estimates and was therefore not considered in the evaluation	d
66	Hayes, R. B. et al. Mortality among benzene-exposed workers in China. Environ Health Perspect 104 Suppl 6, 1349-52 (1996).	YES	YES	NO	NO		d
67	Linet, M. S. et al. Clinical features of hematopoietic malignancies and related disorders among benzene-exposed workers in China. Benzene Study Group. Environ Health Perspect 104 Suppl 6, 1353-64 (1996).	NO			NO		d
68	Mahendra, P., Richards, E. M., Sinclair, P., Nacheva, E. & Marcus, R. E. t(9;13)(q34;q12) chromosomal translocation persisting 4 years post autologous bone marrow transplantation for secondary AML despite morphological remission. Clin Lab Haematol 18, 121-2 (1996).	NO			NO		d
69	Paxton, M. B. Leukemia risk associated with benzene exposure in the Pliofilm cohort. Environ Health Perspect 104 Suppl 6, 1431-6 (1996).	YES	YES	NO	NO		d
70	Raabe, G. K. & Wong, O. Leukemia mortality by cell type in petroleum workers with potential exposure to benzene. Environ Health Perspect 104 Suppl 6, 1381-92 (1996).	NO			NO	Meta analysis	d
71	Rushton, L. Benzene exposure in the petroleum	NO			NO		d

	Citation	Hazard characterization	Quantitative exposure-response analysis specific for benzene and leukemia	Quantitative exposure-response analysis specific for benzene and AML	Included in the evaluation	Remarks	Source
	distribution industry associated with leukemia in the United Kingdom: overview of the methodology of a case-control study. Environ Health Perspect 104 Suppl 6, 1371-4 (1996).						
72	Schnatter, A. R. et al. Lymphohaematopoietic malignancies and quantitative estimates of exposure to benzene in Canadian petroleum distribution workers. Occup Environ Med 53, 773-81 (1996).	YES	YES	NO	NO		d
73	Schnatter, A. R. et al. The relationship between low-level benzene exposure and leukemia in Canadian petroleum distribution workers. Environ Health Perspect 104 Suppl 6, 1375-9 (1996).	YES	YES	NO	NO		d
74	Schnatter, A. R., Nicolich, M. J. & Bird, M. G. Determination of leukemogenic benzene exposure concentrations: refined analyses of the Pliofilm cohort. Risk Anal 16, 833-40 (1996).	YES	YES	YES	NO	This publication performed a re-analysis of the pliofilm data and was therefore not considered in the evaluation	d
75	Yin, S. N. et al. A cohort study of cancer among benzene-exposed workers in China: overall results. Am J Ind Med 29, 227-35 (1996).	YES	NO		NO		d
76	Yin, S. N. et al. An expanded cohort study of cancer among benzene-exposed workers in China. Benzene Study Group. Environ Health Perspect 104 Suppl 6, 1339-41 (1996).	NO			NO		d
77	Collins, J. J., Ireland, B. K., Easterday, P. A., Nair, R. S. & Braun, J. Evaluation of lymphopenia among workers with low-level benzene exposure and the utility of routine data collection. J Occup Environ Med 39, 232-7 (1997).	YES	YES	NO	NO		e
78	**Hayes, R. B. et al. Benzene and the dose-related incidence of hematologic neoplasms in China. Chinese Academy of Preventive Medicine--National Cancer Institute Benzene Study Group. J Natl Cancer Inst 89, 1065-71 (1997).**	**YES**	**YES**	**YES**	**YES**		**b**
79	Ireland, B., Collins, J. J., Buckley, C. F. & Riordan, S. G. Cancer mortality among workers with benzene exposure. Epidemiology 8, 318-20 (1997).	YES	YES	YES	NO	2003 follow up was used	d
80	Lewis, S. J., Bell, G. M., Cordingley, N., Pearlman,	NO			NO		d

	Citation	Hazard characterization	Quantitative exposure-response analysis specific for benzene and leukemia	Quantitative exposure-response analysis specific for benzene and AML	Included in the evaluation	Remarks	Source
	E. D. & Rushton, L. Retrospective estimation of exposure to benzene in a leukaemia case-control study of petroleum marketing and distribution workers in the United Kingdom. Occup Environ Med 54, 167-75 (1997).						
81	Lynge, E., Anttila, A. & Hemminki, K. Organic solvents and cancer. Cancer Causes Control 8, 406-19 (1997).	NO			NO		d
82	**Rushton, L. & Romaniuk, H. A case-control study to investigate the risk of leukaemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom. Occup Environ Med 54, 152-66 (1997).**	**YES**	**YES**	**YES**	**YES**		**d**
83	Nilsson, R. I., Nordlinder, R., Horte, L. G. & Jarvholm, B. Leukaemia, lymphoma, and multiple myeloma in seamen on tankers. Occup Environ Med 55, 517-21 (1998).	YES	NO		NO		d
84	Albin, M. et al. Acute myeloid leukemia and clonal chromosome aberrations in relation to past exposure to organic solvents. Scand J Work Environ Health 26, 482-91 (2000).	YES	NO		NO		b
85	Finkelstein, M. M. Leukemia after exposure to benzene: temporal trends and implications for standards. Am J Ind Med 38, 1-7 (2000).	YES	YES	NO	NO	This publication performed a re-analysis of the pliofilm data and was therefore not considered in the evaluation	d
86	Glass, D. C., Adams, G. G., Manuell, R. W. & Bisby, J. A. Retrospective exposure assessment for benzene in the Australian petroleum industry. Ann Occup Hyg 44, 301-20 (2000).	NO			NO		d
87	Hayes, R. B. et al. Benzene and lymphohematopoietic malignancies in China. J Toxicol Environ Health A 61, 419-32 (2000).	NO			NO		d
88	Korte, J. E., Hertz-Picciotto, I., Schulz, M. R., Ball, L. M. & Duell, E. J. The contribution of benzene to smoking-induced leukemia. Environ Health Perspect 108, 333-9 (2000).	NO			NO		d

	Citation	Hazard characterization	Quantitative exposure-response analysis specific for benzene and leukemia	Quantitative exposure-response analysis specific for benzene and AML	Included in the evaluation	Remarks	Source
89	Schnatter, R. Petroleum worker studies and benzene risk assessment. J Toxicol Environ Health A 61, 433-7 (2000).	NO			NO		d
90	Glass, D. C. & Gray, C. N. Estimating mean exposures from censored data: exposure to benzene in the Australian petroleum industry. Ann Occup Hyg 45, 275-82 (2001).	NO			NO		d
91	Raaschou-Nielsen, O., Hertel, O., Thomsen, B. L. & Olsen, J. H. Air pollution from traffic at the residence of children with cancer. Am J Epidemiol 153, 433-43 (2001).	YES	YES	NO	NO		d
92	**Guenel, P., Imbernon, E., Chevalier, A., Crinquand-Calastreng, A. & Goldberg, M. Leukemia in relation to occupational exposures to benzene and other agents: a case-control study nested in a cohort of gas and electric utility workers. Am J Ind Med 42, 87-97 (2002).**	**YES**	**YES**	**YES**	**YES**		**d**
93	Li, K. & Yu, S. Leukemia mortality and occupational exposure to rubber: a nested case-control study. Int J Hyg Environ Health 204, 317-21 (2002).	YES	NO		NO		d
94	Rinsky, R. A., Hornung, R. W., Silver, S. R. & Tseng, C. Y. Benzene exposure and hematopoietic mortality: A long-term epidemiologic risk assessment. Am J Ind Med 42, 474-80 (2002).	YES	YES	NO	NO		d
95	Silver, S. R., Rinsky, R. A., Cooper, S. P., Hornung, R. W. & Lai, D. Effect of follow-up time on risk estimates: a longitudinal examination of the relative risks of leukemia and multiple myeloma in a rubber hydrochloride cohort. Am J Ind Med 42, 481-9 (2002).	YES	YES	NO	NO		d
96	Adegoke, O. J. et al. Occupational history and exposure and the risk of adult leukemia in Shanghai. Ann Epidemiol 13, 485-94 (2003).	YES	NO		NO		b
97	**Collins, J. J., Ireland, B., Buckley, C. F. & Shepperly, D. Lymphohaematopoeitic cancer mortality among workers with benzene exposure. Occup Environ Med 60, 676-9 (2003).**	**YES**	**YES**	**YES**	**YES**		**b**
98	**Glass, D. C. et al. Leukemia risk associated with**	**YES**	**YES**	**YES**	**YES**		**d**

	Citation	Hazard characterization	Quantitative exposure-response analysis specific for benzene and leukemia	Quantitative exposure-response analysis specific for benzene and AML	Included in the evaluation	Remarks	Source
	low-level benzene exposure. Epidemiology 14, 569-77 (2003).						
99	Seniori Costantini, A., Quinn, M., Consonni, D. & Zappa, M. Exposure to benzene and risk of leukemia among shoe factory workers. Scand J Work Environ Health 29, 51-9 (2003).	YES	YES	NO	NO		d
100	Adegoke, O. J. et al. Agreement of job-exposure matrix (JEM) assessed exposure and self-reported exposure among adult leukemia patients and controls in Shanghai. Am J Ind Med 45, 281-8 (2004).	NO			NO		d
101	**Bloemen, L. J., Youk, A., Bradley, T. D., Bodner, K. M. & Marsh, G. Lymphohaematopoietic cancer risk among chemical workers exposed to benzene. Occup Environ Med 61, 270-4 (2004).**	**YES**	**YES**	**YES**	**YES**		**d**
102	Crosignani, P. et al. Childhood leukemia and road traffic: A population-based case-control study. Int J Cancer 108, 596-9 (2004).	YES	YES	NO	NO		d
103	Glass, D. C. et al. Leukemia risk and relevant benzene exposure period-Re: follow-up time on risk estimates, Am J Ind Med 42:481-489, 2002. Am J Ind Med 45, 222-3; author reply 224-5 (2004).	NO			NO		d
104	Patel, A. S. et al. Risk of cancer as a result of community exposure to gasoline vapors. Arch Environ Health 59, 497-503 (2004).	YES	NO		NO		d
105	Steffen, C. et al. Acute childhood leukaemia and environmental exposure to potential sources of benzene and other hydrocarbons; a case-control study. Occup Environ Med 61, 773-8 (2004).	YES	NO		NO		d
106	Glass, D. C., Gray, C. N., Jolley, D. J., Gibbons, C. & Sim, M. R. Health Watch exposure estimates: do they underestimate benzene exposure? Chem Biol Interact 153-154, 23-32 (2005).	NO			NO		d
107	Kasim, K., Levallois, P., Abdous, B., Auger, P. & Johnson, K. C. Lifestyle factors and the risk of adult leukemia in Canada. Cancer Causes Control 16, 489-500 (2005).	YES	NO		NO		d

	Citation	Hazard characterization	Quantitative exposure-response analysis specific for benzene and leukemia	Quantitative exposure-response analysis specific for benzene and AML	Included in the evaluation	Remarks	Source
108	Mirer, F. E. Comment on Caprolactam study. Ann Epidemiol 15, 735; author reply 736 (2005).	NO			NO		d
109	Schnatter, A. R., Rosamilia, K. & Wojcik, N. C. Review of the literature on benzene exposure and leukemia subtypes. Chem Biol Interact 153-154, 9-21 (2005).	NO			NO		d
110	Sorahan, T., Kinlen, L. J. & Doll, R. Cancer risks in a historical UK cohort of benzene exposed workers. Occup Environ Med 62, 231-6 (2005).	YES	NO		NO		d
111	Swaen, G. M., Scheffers, T., de Cock, J., Slangen, J. & Drooge, H. Leukemia risk in caprolactam workers exposed to benzene. Ann Epidemiol 15, 21-8 (2005).	YES	YES	NO	NO		d
112	Glass, D. C., Gray, C. N., Jolley, D. J., Gibbons, C. & Sim, M. R. The health watch case-control study of leukemia and benzene: the story so far. Ann N Y Acad Sci 1076, 80-9 (2006).	NO			NO		d
113	Li, G. & Yin, S. Progress of epidemiological and molecular epidemiological studies on benzene in China. Ann N Y Acad Sci 1076, 800-9 (2006).	NO			NO		d
114	Wiwanitkit, V. Classification of risk occupation for benzene exposure by urine trans, trans-munconic acid level. Asian Pac J Cancer Prev 7, 149-50 (2006).	YES	NO		NO		d
115	Schubauer-Berigan, M. K. et al. Risk of chronic myeloid and acute leukemia mortality after exposure to ionizing radiation among workers at four U.S. nuclear weapons facilities and a nuclear naval shipyard. Radiat Res 167, 222-32 (2007).	YES	NO		NO		d
116	Zhang, L. et al. Aberrations in chromosomes associated with lymphoma and therapy-related leukemia in benzene-exposed workers. Environ Mol Mutagen 48, 467-74 (2007).	YES	NO		NO		d

[a] Referenced in 1995 risk assessment by Canadian Centre for Occupational Health and Safety (CCOHS) http://www.canoshweb.org/odp/html/rp7.htm (accessed on 02/12/2008) [b] Referenced in literature by Schnatter et al. (Schnatter, A. R., Rosamilia, K. & Wojcik, N. C. Review of the literature on benzene exposure and leukemia subtypes. Chem Biol Interact 153-154, 9-21 (2005) [c] Referenced in 1976 risk assessment by NIOSH http://www.cdc.gov/niosh/pdfs/76-benz.pdf (accessed on 02/12/2008)
[d] Pubmed search including the following MESH keywords: *benzene, humans, leukaemia* in combination with either *cohort studies* or case- *studies* (performed on 02/12/2008)
[e] Referenced in 2007 literature review by U.S. Agency for Toxic Substances and Disease Registry (ATSDR) http://www.atsdr.cdc.gov/toxprofiles/tp3.pdf (accessed on

02/12/2008) [f] Referenced in risk assessment by U.S. EPA 'Carcinogenic Effects of Benzene: an Update' (1998) http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=2806 (accessed on 02/12/2008)

Supplemental Material III: Outcome of the Evaluation of the Studies that were Eligible for Evaluation with the Guidelines

(1) AUSTRALIAN HEALTH WATCH STUDY		
Evaluated papers	1. Glass, D. C., Adams, G. G., Manuell, R. W. & Bisby, J. A. Retrospective exposure assessment for benzene in the Australian petroleum industry. Ann Occup Hyg 44, 301-20 (2000). 2. Glass, D. C. et al. Leukemia risk associated with low-level benzene exposure. Epidemiology 14, 569-77 (2003). 3. Glass, D. C., Gray, C. N., Jolley, D. J., Gibbons, C. & Sim, M. R. Health Watch exposure estimates: do they underestimate benzene exposure? Chem Biol Interact 153-154, 23-32 (2005).	
Criteria	**Description**	**Outcome**
T1.1	A case-control design was used in this study	Yes
T1.2	Exposure was expressed on a ratio scale and specific for benzene	Yes
T1.3	Sufficient details were provided regarding the performed statistical analysis (Conditional logistic regression)	Yes
T1.4	Criteria for inclusion of subjects were described with sufficient detail. Inclusion criteria for cases were: sex = male, member of the Health Watch cohort and reported and confirmed lympho-hematopoietic cancer. Controls were randomly selected from the Health Watch cohort and matched to the cases based on year of birth	Yes
T1.5	Assessment of the health effect was performed following recognized norms. A hierarchical classification strategy was applied in which histological confirmation of AML was considered to be a higher level of evidence than classification based on a doctor's letter, which was considered to be a higher level of evidence than information from the cancer registry, which was considered to be a higher level of evidence than information from a death certificate	Yes
T1.6	Ionizing radiation is not considered as potential strong confounder in this study. It is assumed that the level of ionizing radiation received by the studied workers is on background level. Other factors were tested for a potential association with total leukemia: tobacco smoking, drinking alcohol, duration of employment and employment starting date	Yes
T2.1	This study was conducted following a case-control design nested in the Health Watch cohort	
T3.1	The response rate of this study was 100%	
T3.4	The quality of the methods for exposure measurements and criteria for inclusion and exclusion and limitations of exposure measurements were discussed. Results from exposure measurements were used for exposure assessment if personal exposure measurements were performed, if measurements were not corrected to 8 hour time weighted averages and if information on job site-location, job title and duration of monitoring was available for the measurements. In addition, exposure measurements were not used for exposure assessment if adequate information on the used measuring method was not available, if no units were presented, if no information on the year of measurement was available, if detailed information regarding the measured tasks was not available, if the purpose of the measurement was not specified and if information whether the measured exposure situation was typical for the assessed task was not available. Limitations of the exposure measurements used for exposure assessment were discussed as well. More frequently occurring limitations were: no information on the limit of detection, no information on the technology used for exposure measurements, no information on the type of products that were handled by the measured worker and limited information on the specificity of the measurements for the measurement site	
T3.5	The variability in exposure measurements and potential for measurement error was not discussed	
T3.6	Task based exposure measurements were used to generate a workplace exposure estimate defined as the 'time weighted average of different activity	

	exposures normalized to 35 hour work week'. Exposure modifying factors were applied to the exposure measurements in order to estimate exposures for workplaces and time periods for which no exposure measurements were available	
T3.7	The reported exposure metrics included cumulative lifetime exposure (ppm-years)	
T3.8	Benzene concentration (causal agent) in the breathing zone (external exposure) was used as indicator of exposure	Causal / External
T3.9	It was reported that the occupational hygienists performing the exposure assessment did so without knowledge of the case or control status of the subjects	
T3.10	Exposure was assigned based on the jobs workers performed during their lifetime. For each job title a workplace exposure estimate was multiplied with the years spent in a specific job. The estimates for specific job-titles were aggregated into cumulative lifetime exposure. In addition, the level of extrapolation needed to assign measured exposures to the individuals in the studied population was discussed	
T3.11	Because both cases and controls were selected from the Health Watch cohort it is assumed that there was limited potential for information bias	
T3.13	No sensitivity analysis was performed	

(2) CAPM-NCI STUDY		
Evaluated papers	1. Yin, S. N. et al. Cohort study among workers exposed to benzene in China: I. General methods and resources. Am J Ind Med 26, 383-400 (1994). 2. Dosemeci, M. et al. Cohort study among workers exposed to benzene in China: II. Exposure assessment. Am J Ind Med 26, 401-11 (1994). 3. Travis, L. B. et al. Hematopoietic malignancies and related disorders among benzene-exposed workers in China. Leuk Lymphoma 14, 91-102 (1994). 4. Hayes, R. B. et al. Benzene and the dose-related incidence of hematologic neoplasms in China. Chinese Academy of Preventive Medicine--National Cancer Institute Benzene Study Group. J Natl Cancer Inst 89, 1065-71 (1997).	
Criteria	**Description**	**Outcome**
T1.1	A cohort design was used in this study	Yes
T1.2	Exposure was expressed on a ratio scale and specific for benzene	Yes
T1.3	Sufficient details were provided regarding the performed statistical analysis (Poisson regression analysis)	Yes
T1.4	Criteria for inclusion of subjects were described with sufficient detail. Included workers were employed in 672 factories in 12 cities in China	Yes
T1.5	An extensive method for the classification of the health outcome was used. The method included evaluation of medical records, pathology reports and histopathological material	Yes
T1.6	Ionizing radiation was not considered as potential strong confounder in this study. It is assumed that the level of ionizing radiation received by the individuals in the studied population is on background level	Yes
T2.1	This study was conducted following a cohort design	
T3.1	The response rate of this study was 100 %	
T3.2	The loss to follow-up reported in this study was 0.2% for exposed individuals and 0.3 % for unexposed individuals	
T3.3	The average follow up time in this study was 10.5 years for individuals exposed to benzene and 11.7 years for individuals not exposed to benzene	
T3.4	Although the number of exposure measurements used for exposure assessment was reported, there was limited insight in the quality of these measurements. It was reported that most of the benzene measurements were based on short-term area sampling and that there was a lack of personal sampling	
T3.5	There was limited discussion on the variability in exposure measurements. The mean concentration of the available exposure measurements was reported for seven calendar periods. This provides some insight in the variability of exposure over time. The potential for measurement error in the exposure measurements was not discussed	
T3.6	For each combination of job-title and time-period, exposure was estimated based on estimates by local industrial hygienist and other occupational health personnel. The experts used the available ambient benzene exposure measurements in combination with detailed production and related process information for seven calendar periods	
T3.7	The reported exposure metrics included cumulative lifetime exposure (ppm-years) and average exposure (ppm)	
T3.8	Benzene concentration (causal agent) in the breathing zone (external exposure) was used as indicator of exposure	Causal / External
T3.9	Exposure assessment was performed on the level of factory/work unit/job title/calendar-year. Only in the assignment stage were results from exposure assessment linked to the individuals in the study population based on work histories. It is therefore assumed that exposure assessment was performed blinded for the disease status of the individuals in the population	
T3.10	Exposure was assigned to individuals in the study population based on the jobs that were performed in their work history	
T3.11	There was no difference in the level of information available for exposed individuals and unexposed individuals. Therefore it is assumed that the potential for information bias was low	

T3.12	It was reported that clinical laboratory and pathology data for all patients were abstracted onto standardized forms by physician investigators who were not aware of the exposure status of the subjects, nor of the numbers of exposed and non-exposed cases	
T3.13	No sensitivity analysis was performed	

(3) DOW COHORT STUDY		
Evaluated papers	1. Ott, M. G., Townsend, J. C., Fishbeck, W. A. & Langner, R. A. Mortality among individuals occupationally exposed to benzene. Arch Environ Health 33, 3-10 (1978). 2. Bloemen, L. J., Youk, A., Bradley, T. D., Bodner, K. M. & Marsh, G. Lymphohaematopoietic cancer risk among chemical workers exposed to benzene. Occup Environ Med 61, 270-4 (2004).	
Criteria	**Description**	**Outcome**
T1.1	A cohort design was used in this study	Yes
T1.2	Exposure was expressed on a ratio scale and specific for benzene	Yes
T1.3	Sufficient details were provided regarding the performed statistical analysis (OCMAP-PLUS modified life table procedure)	Yes
T1.4	Criteria for inclusion of subjects were described with sufficient detail. Employees with at least one month's work experience in any of three relevant production areas on or after 1 january 1938 were included in the study	Yes
T1.5	Assessment of the health effect was performed following recognized norms. Cause of death was determined based on a death certificate and was coded by a certified nosologist according to the ICD in effect at the time of death. For this study all original codifications were recoded to ICD-9	Yes
T1.6	Ionizing radiation was not considered as potential strong confounder in this study. It is assumed that the level of ionizing radiation received by the individuals in the studied population is on background level	Yes
T2.1	This study was conducted following a cohort design	
T3.1	The response rate of this study was 100 %	
T3.2	The loss to follow-up reported in this study was 0.6 %	
T3.3	68% of the members of the cohort were followed at least 30 years	
T3.4	The quality criteria for exposure measurements to be included in the exposure assessment were not discussed	
T3.5	The number of exposure measurements, range of the measurements and estimated time weighted averages were presented. But these results were not discussed in the text	
T3.6	The relation between job-title and time period specific exposure estimates and the use of industrial hygiene measurements is unclear. Job-titles were assigned to exposure categories by an industrial hygienist. The exposure categories were based on the industrial hygiene measurements reported in the 1978 study	
T3.7	The reported exposure metrics included cumulative lifetime exposure (ppm-years) and average exposure (ppm)	
T3.8	Benzene concentration (causal agent) in the breathing zone (external exposure) was used as indicator of exposure	Causal / External
T3.9	Exposure assessment was performed on the level of job title/time-period. Only in the assignment stage were results from exposure assessment linked to the individuals in the study population based on work histories. It is therefore assumed that exposure assessment was performed blinded for the disease status of the individuals in the population	
T3.10	Individual employee histories were linked to job and time specific benzene exposure estimates to compute the summary exposure measures	
T3.11	The exposed population is compared to a local population which is assumed to be exposed at background level. Therefore, some potential for information bias regarding health outcome assessment exists	
T3.12	The cause of death was derived from company human resource records or population mortality registries. Therefore the health outcome assessment is assumed to have been performed blinded for the exposure status	
T3.13	No sensitivity analysis was performed	

(4) GUÉNEL STUDY		
Evaluated papers	1. Guenel, P., Imbernon, E., Chevalier, A., Crinquand-Calastreng, A. & Goldberg, M. Leukemia in relation to occupational exposures to benzene and other agents: a case-control study nested in a cohort of gas and electric utility workers. Am J Ind Med 42, 87-97 (2002).	
Criteria	**Description**	**Outcome**
T1.1	A case-control design was used in this study	Yes
T1.2	Exposure was not expressed on a ratio scale but presented in unit-years.	No, **Study should be excluded from QRA**
T1.3	Sufficient details were provided regarding the performed statistical analysis (Unadjusted conditional logistic regression)	Yes
T1.4	Criteria for inclusion of subjects were described with sufficient detail. Cases were workers diagnosed with leukemia active at the time of diagnosis. For each case 4 controls were selected. The controls were also active EDF-GDF workers matched to the cases by year of birth	Yes
T1.5	Assessment of the health effect was performed following recognized norms. A pathology report was used to code cases following ICD-O	Yes
T1.6	Ionizing radiation was not considered as potential strong confounder in this study. It is assumed that the level of ionizing radiation received by the studied workers is on background level. In addition, there is no indication that the cases in this study are differently exposed to ionizing radiation than the controls	Yes

(5) MONSANTO COHORT STUDY		
Evaluated papers	1. Ireland, B., Collins, J. J., Buckley, C. F. & Riordan, S. G. Cancer mortality among workers with benzene exposure. Epidemiology 8, 318-20 (1997). 2. Collins, J. J., Ireland, B., Buckley, C. F. & Shepperly, D. Lymphohaematopoeitic cancer mortality among workers with benzene exposure. Occup Environ Med 60, 676-9 (2003).	
Criteria	**Description**	**Outcome**
T1.1	A cohort design was used in this study	Yes
T1.2	Exposure was expressed on a ratio scale and specific for benzene	Yes
T1.3	Insufficient details were provided regarding the performed statistical analysis in this study. Therefore, there is no insight in the decisions that were made in the statistical analysis (e.g. stratification for age and time period)	No, **Study should be excluded from QRA**
T1.4	The criteria for inclusion of subjects were described with sufficient detail. The study population consisted of all hourly workers that began employment between 1940 and 1977 at the Monsanto (Solutia) plant	Yes
T1.5	Assessment of the health effect was performed following recognized norms. Death certificates were used to assess the health effect	Yes
T1.6	Ionizing radiation was not considered as potential strong confounder in this study. It is assumed that the level of ionizing radiation received by the individuals in the studied population is on background level	Yes

	(6) PLIOFILM COHORT STUDY	
Evaluated papers	1. Rinsky, R. A. et al. Benzene and leukemia. An epidemiologic risk assessment. N Engl J Med 316, 1044-50 (1987). 2. Rinsky, R. A. Benzene and leukemia: an epidemiologic risk assessment. Environ Health Perspect 82, 189-91 (1989). 3. Paxton, M. B., Chinchilli, V. M., Brett, S. M. & Rodricks, J. V. Leukemia risk associated with benzene exposure in the pliofilm cohort: I. Mortality update and exposure distribution. Risk Anal 14, 147-54 (1994a). 4. Paxton, M. B., Chinchilli, V. M., Brett, S. M. & Rodricks, J. V. Leukemia risk associated with benzene exposure in the pliofilm cohort. II. Risk estimates. Risk Anal 14, 155-61 (1994b). 5. Wong, O. Risk of acute myeloid leukaemia and multiple myeloma in workers exposed to benzene. Occup Environ Med 52, 380-4 (1995).	
Criteria	**Description**	**Outcome**
T1.1	A cohort design was used in this study	Yes
T1.2	Exposure was expressed on a ratio scale and specific for benzene	Yes
T1.3	Sufficient details were provided regarding the performed statistical analysis (Standardized mortality ratios were calculated with the NIOSH lifetable analysis program)	Yes
T1.4	Criteria for inclusion of subjects were described with sufficient detail. All nonsalaried white men employed in a rubber hydrochloride department for at least one day between jan 1, 1940 and December 31, 1965 were included in the study population	Yes
T1.5	Assessment of the health effect was performed following recognized norms. Health effect classification was based on death certificates and codification by a qualified nosologist	Yes
T1.6	Ionizing radiation was not considered as potential strong confounder in this study. It is assumed that the level of ionizing radiation received by the individuals in the studied population is on background level	Yes
T2.1	This study was conducted following a cohort design.	
T3.1	The response rate of this study was 100 %	
T3.2	The loss to follow-up reported in this study was 0.9%	
T3.3	A minimum follow-up time of 22 years was reported in this study	
T3.4	Industrial hygiene measurements were used for exposure assessment. Limited discussion regarding the quality of the measurements and the number of measurements that was available is presented in the reviewed papers. However, it was mentioned that industrial hygiene measurements consisted primarily of area samples and not personal samples	
T3.5	Variability in exposure measurements and the potential for measurement error was not discussed	
T3.6	Job titles were grouped into exposure classes. In general exposure classes represented areas in which industrial-hygiene data had been collected. In some instances, job titles did not readily fit into a single area; in such situations hybrid classes were defined. Cells were defined based on an exposure class-year combination. Cells for which no data was available were completed by interpolation between available previous and subsequent values. When interpolation could not be performed because no measured value existed for an exposure class in the first or last year of the study, the nearest measured value for that exposure class was projected forward or backward	
T3.7	The reported exposure metrics included cumulative lifetime exposure (ppm-years)	
T3.8	Benzene concentration (causal agent) in the breathing zone (external exposure) was used as indicator of exposure	Causal / External
T3.9	Exposure assessment was performed on the level of ‘exposure class’. Only in the assignment stage were results from exposure assessment linked to the individuals in the study population based on work histories. It is therefore assumed that exposure assessment was performed blinded	

	for the disease status of the individuals in the population	
T3.10	Person's daily benzene exposure was obtained from the appropriate cell in the exposure class-year matrix. These daily values were then summed for a workers entire career	
T3.11	Mortality in studied population was compared to mortality in the general population for which background exposure levels were assumed. Therefore there is some potential for information bias	
T3.12	There was no specific mention of blinded health outcome assessment	
T3.13	No sensitivity analysis was performed	

(7) U.K. PETROLEUM WORKERS STUDY		
Included papers	1. Rushton, L. & Romaniuk, H. A case-control study to investigate the risk of leukaemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom. Occup Environ Med 54, 152-66 (1997). 2. Lewis, S. J., Bell, G. M., Cordingley, N., Pearlman, E. D. & Rushton, L. Retrospective estimation of exposure to benzene in a leukaemia case-control study of petroleum marketing and distribution workers in the United Kingdom. Occup Environ Med 54, 167-75 (1997).	
Criteria	**Description**	**Outcome**
T1.1	A case-control design was used in this study	Yes
T1.2	Exposure was expressed on a ratio scale and specific for benzene	Yes
T1.3	Sufficient details were provided regarding the performed statistical analysis.(various different statistical approaches were applied)	Yes
T1.4	Criteria for inclusion of subjects were described with sufficient detail. Cases were men from UK oil distribution cohort who died before 1 january 1993 with a mention of leukemia on their death certificate or had an ICD-9 code 204-208 in the cancer registry. Controls were randomly selected from the same cohort and were matched to the cases based on age	Yes
T1.5	Assessment of the health effect was performed following recognized norms. Information from death certificates and information from a cancer registry was used. If the information from the two sources was conflicting information from the death certificate overruled information from the cancer registry	Yes
T1.6	Ionizing radiation was not considered as potential strong confounder in this study. It is assumed that the level of ionizing radiation received by the individuals in the studied population is on background level	Yes
T2.1	In this study a nested case-control design was used	
T3.1	The response rate of this study was 100 %	
T3.4	The quality of the exposure measurements used in the exposure assessment was discussed. The discussion was focused on the quality of the exposure measurements, the validity of the used sampling technologies and the used analytical techniques. The authors reported that only high quality personal exposure measurements were used for exposure assessment	
T3.5	The distribution of benzene exposure measurements originating from similar exposure contexts was assessed and tested for log-normality. The potential for measurement error due to inaccuracy of the used measurement techniques was not discussed	
T3.6	Retrospective estimates of workplace exposure for each job reported in the work histories of all the study members were obtained by creating base estimates. Base estimates were estimated based on the exposure measurements and adjusted with the use of modifying factors. Modifying factors represented factors that could have affected the exposure levels (e.g. changes in exposure circumstances over time or between two different work-sites)	
3.7	The reported exposure metrics included cumulative lifetime exposure (ppm-years)	
T3.8	Benzene concentration (causal agent) in the breathing zone (external exposure) was used as indicator of exposure	Causal / External
T3.9	Exposure assessment was performed on the level of workplace. Only in the assignment stage were results from exposure assessment linked to the individuals in the study population based on work histories. It is therefore assumed that exposure assessment was performed blinded for the disease status of the individuals in the population	
T3.10	Cumulative lifetime exposure was estimated by summing the cumulative exposure for each different job held by an individual for the individuals entire work history	

T3.11	Potential for information bias was tested with a sensitivity analysis and was reported to be low	
T3.13	A sensitivity analysis was performed to test the influence of several factors on the study outcomes	